31. (previously presented) The method of Claim 30 wherein the sample is fragmented to generate said different RNAs from a plurality of target RNAs.

REMARKS

Applicants have amended Claims 1 to more clearly point out the claimed invention. Amended claim 1 recites "target regions of the probes are distributed along the mRNAs." Support for this amendment can be found, for example, in lines 13-14, page 19 of the specification. Applicants respectfully submit that no new matter is presented by the amendments and respectfully request entry of the same. Applicants do not acquiesce to the propriety of any of the Examiner's rejections nor disclaim any subject matter to which they are entitled by these amendments.

Claim Rejections under 35 U.S.C. § 112 should be withdrawn

Claims 1-20 and 24-31 have been rejected under 35 U.S.C §112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner specifically alleged that the specification does not provide adequate support for extension of substantially full length mRNAs and detection of substantially full length mRNAs. Applicants respectfully disagree with the Examiner. However, solely to expedite the issuance of the present claims, Applicants have amended Claim 1 to recite "target regions of the probes are distributed along the mRNAs".

In summary in view of the above Claim amendment, Applicants respectfully submit that the rejection of Claim 1 and dependent Claims 2-20 and 24-30 under 35 U.S.C §112, first and second paragraphs, is obviated.

Claim Rejections under 35 U.S.C. § 102 should be withdrawn

Claims 1-5, 24, 25, 30 and 31 are rejected under 35 U.S.C. §102 (a) as allegedly being anticipated by Weidenhammer et al. (US Patent No. 6,379,897). Applicants respectfully disagree with the Office Action. Weidenhammer et al. teach a method of detecting shortened **amplicons** i.e. short **amplified** RNA or cDNA molecules (see col. 14 lines 16-46 and definition of amplicons col. 6, line 50-60). Weidenhammer et al. extensively discuss how after isolation of mRNA, "reverse transcription is performed to generate single stranded cDNAs from the mRNA population" (see col. 8, lines 22-38). cDNAs are then amplified linearly to allow quantitative comparison between samples (See col. 4, lines 47-49). Amplicons are shortened by enzymatic digestion or bookending and target fragments are used as template for multiple in vitro transcription rounds to generate **shortened cRNAs** (see Figure 1 and col. 11, lines 30-58). Shortened cRNA amplicons are hybridized to a microarray of probes and incubated with reagents that allow primer extension of the capture probe using the bound amplicons as a target. Weidenhammer et al. does not teach direct hybridization of mRNAs to a microarray of oligonucleotide probes. The method discussed by Weidenhammer et al. is 3' biased because it includes a reverse transcription step using polythymine primers (col. 8 lines 22-38). The claimed invention provides a method that overcomes the 3' bias inherent of the method discussed by Weidenhammer et al. by **directly** hybridizing target mRNAs to

a microarray of probes that are suitable for primer extension, synthesizing primer extension products with a nucleic acid polymerase, wherein the primer extension products comprise 5' regions of the transcripts and detecting bound RNAs using a label. The probes-primers used for primer extension in the claimed invention may be selected to cover the entire RNA sequences therefore enabling the interrogation biologically relevant information in the entire RNAs sequences (see page 19, lines 11-20).

Applicants respectfully submit that in view of the above amendment and remarks, the rejection of Claims 1-5, 24, 25, 30 and 31 under 35 U.S.C. §102 (a) should be withdrawn.

Claim Rejections under 35 U.S.C. § 103 should be withdrawn

Claims 6-20 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weidenhammer et al. (US Patent No. 6,379,897) in view of Heller et al. (U.S. Patent No. 5,605,662).

As discussed above, the primary reference Weidenhammer et al. fails to teach all of the claim limitations of claims 6-20. Weidenhammer fails to teach, suggest or motivate hybridizing RNA molecules that have not been previously reverse transcribed and amplified onto a microarray of probe-primers for extension. Heller et al. is cited as providing additional features such as the synthesis of probes on substrate within the microlocations of size 50 μm by 50 μm and does not remedy to the deficiency of the primary reference. Applicants respectfully request that the rejection of Claims 6-20 under 35 U.S.C. § 103 (a) should be withdrawn.

Claims 26-29 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Weidenhammer et al. in view of Heller et al. and further in view of Chee et al. (U.S. Patent No. 5,837,832).

Weidenhammer et al. in view of Heller et al. fail to teach all of the claim limitations of claims 26-29. Chee et al. is cited as providing additional features such as teaching tiling and fails to remedy the deficiencies of Weidenhammer et al. in view of Heller et al. Therefore, Applicants respectfully request that the rejection of Claims 26-29 under 35 U.S.C. § 103 (a) should be withdrawn.

In summary, since the cited references, alone or in combination, do not teach or suggest the present invention, Applicants respectfully submit that the Office Action failed to establish a prima facie case of obviousness for the instant claims. Therefore, the rejection of Claims 6-20 and 26-29 under 35 USC § 103(a) should be withdrawn.

Serial No.: 09/746,113
Attorney Docket No.: 3375

CONCLUSION

For these reasons, Applicants believe all pending claims are now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

If the Examiner has any questions pertaining to this application, the Examiner is requested to contact the undersigned agent.

Respectfully submitted,

Dated: November 24, 2004

Wei Zhou Reg. No. 44,419

Customer No. 22886
Legal Department
Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051
Tel: 408/731-5000
Fax: 408/731-5392